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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,919	12/06/2001	C. Frank Bennett	RTS-0256	7597

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,919	BENNETT ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed September 27, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed June 24, 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant's election without traverse of Group I, and also SEQ ID NO: 21, in the reply filed on April 12, 2004 is again acknowledged.

SEQ ID NOS: 10-20, 22-28, 30-56, 58, 59, 61, 62, 66, 67, 69, 70, 73-76, 79, and 81-87, of claim 3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 12, 2004.

Specification

The disclosure is objected to because of the following informalities: On page 3, line 6 of the instant specification, U. S. Patent Number 6,283,903 is referred to, and referenced as the U. S. Patent issued to Krystal et al. However, in applicant's IDS submitted June 24, 2004, the patent

issued to Krystal et al. is listed as U. S. Patent Number 6,238,903. Internal USPTO records list the U. S. Patent issued to Krystal et al. as 6,238,903.

Appropriate correction is required.

Response to Claim Rejections - 35 USC § 103

Claims 1, 2, and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohrschneider *et al.*, in view of Ware *et al.*, Taylor et al., and Baracchini et al. (all of record), and is repeated for the same reasons of record as set forth in the Official action mailed June 24, 2004.

Applicants have traversed the instant rejection by asserting that the combination of art does not provide a motivation or teaching to combine the teachings to produce the claimed invention. Applicants argue that the reference of Rohrschneider provides "only a very generalized goal to prepare antisense oligonucleotides targeted to an unidentified Ship-1 sequence of SEQ ID NO: 3 for inhibition of expression", because Rohrschneider fails to provide specific explanation, guidance, or examples of how to design antisense oligos or their phosphorothioate analogues, and further does not suggest making antisense compounds that comprise pharmaceutically acceptable compositions.

These arguments are not considered convincing, because they are based on a mis-characterization of the Rohrschneider reference, and furthermore these arguments represent a piecemeal analysis of the Rohrschneider reference which ignores teachings from the other references that form the basis of the instant rejection. Rohrschneider specifically teach a genus of

antisense molecules that target and inhibit the expression of Ship, and further teach such molecules as they are modified, i.e. phosphorothioated.

As a first note, applicants are reminded that the instantly claimed invention is not drawn to any specific antisense oligo as implied, but rather to the genus of any antisense oligo targeted to Ship-1. Rohrschneider teach the genus of phosphorothioated oligonucleotides targeted to Ship (see pages 48-52), wherein applicants' specification indicates Ship is identical to Ship-1 (see specification, page 2 lines 7-9). The only reason that Rohrschneider et al. is not considered a reference under 35 U.S.C. § 102(b) is because while Rohrschneider et al. provides the identically named target of Ship-1, Rohrschneider et does not provide the actual sequence of SEQ ID NO: as instantly claimed. However, the sequence of SEQ ID NO: 3 is taught by Ware et al., which was included in this rejection. Although Rohrschneider does not provide the actual sequences of the individual oligos, both Taylor et al. and Baracchini et al. teach that with the sequence in hand, one of ordinary skill can easily design antisense sequences that inhibit their target. Since Rohrschneider specifically teaches the genus of phosphorothioated antisense oligonucleotides targeted to Ship, applicants appear to be mistaken in their belief that a mere "generalized goal" is presented by Rohrschneider to make phosphorothioated antisense molecules targeted to Ship.

Regarding applicants contention that Rohrschneider fails to provide specific explanation, guidance, or examples on how to design antisense oligos or their phosphorothioate analogues, applicants are reminded that this is a rejection under 35 U.S.C. § 103(a), not under 35 U.S.C. § 102(b). The blueprint of how to make antisense comes from the combination of Taylor, who says that antisense can be easily designed provided the sequence is known (which it is, taught by Ware et al.), and Baracchini who teach designing oligos and assays useful for testing antisense

activity. What Rohrschneider provides is a specific teaching of modified antisense oligos targeted to ship-1. None of Baracchini, Ware or Taylor et al. are relied upon for such a teaching of motivation. Ware was relied upon to show that the Ship-1 sequence of applicants' instant SEQ ID NO: 3 was known, and Taylor et al. and Baracchini et al. were relied upon to show that one could reasonably expect to find an oligo within the genus of those taught by Rohrschneider that inhibits its target.

Regarding whether the instant combination of references provides the information necessary for a reasonable expectation of success, applicants argue that the combination of cited references fails to provide direction as to which of many possible choices of Ship-1 antisense molecules targeted to SEQ ID NO:3 are likely to be successful, which therefore renders the instant invention "obvious to try."

Applicants are mistaken in their belief that the instant references do not provide a reasonable expectation of success. As a first matter, applicants suggest that in order for a claim to the genus of antisense molecules targeting Ship-1 to be considered obvious, that one must be able to predict what the sequence of such an antisense molecule will be. Applicants are directed to the language of the instantly rejected claims, which are notable for not actually claiming a specific sequence, but are rather directed to the genus of any sequence that targets and inhibits Ship-1. Because the claimed invention is not directed to a specific sequence, it is not necessary to predict whether one particular sequence will be inhibitory. The reasonable expectation clause applies in this case to whether one of ordinary skill could reasonably expect to find an antisense molecule 8 to 50 nucleobases in length targeted to Ship-1 of SEQ ID NO: 3, wherein said antisense inhibits the expression of Ship-1. It is maintained that Baracchini et al. and Taylor et al.

provide such an expectation, which is explained in more detail below.

Applicants allege that Taylor et al. teaches that one of skill cannot predict specific active sequences without experimentation. Whether or not this is actually true is irrelevant, because as implied above, the test is whether one would have a reasonable expectation of achieving an antisense compound that falls within the claimed genus of molecules that inhibit its target.

To this, applicants argue that Taylor statement that "only 3-6 sequences need to be screened in order to find one that inhibits 66-95% *in vitro*" does not assist one of ordinary skill how to design antisense oligos because the antisense oligos and the target sequence are not named by Taylor, and because the specific program used by Taylor is referenced as "unpublished data". However, keeping in mind that the test of reasonable expectation applies to the claimed invention, which is not a specific sequence, but rather the genus of any antisense molecules that target and inhibit Ship-1, applicants are directed to the entire paragraph in the cited Taylor reference:

> The best target sites are still determined empirically, although improvements in the potency of ONs [oligonucleotides] and in the algorithms used for predicting accessible sites on the target mRNA have drastically reduced the number of oligonucleotides that must be screened to find one that is effective. Previous recommendations required the screening of 30-60 ONs per gene. Using high affinity chimeric oligomers and a bioinfonnatic program to select accessible sites, Woolf and coworkers have found that screening 3-6 oligomers per target is sufficient to find one that inhibits the gene with 66-95%.

Taylor et al. is relied upon merely to indicate that such screening is considered to be routine. For the actual method steps of the screens, applicants are directed to the teachings of Baracchini, who provide explicit detailed directions on how to design and screen molecules for specific levels of inhibitory activity, complete with precise protocols of how to make and use antisense oligos to inhibit a gene of known sequence, including materials related to synthesis of such

oligos *de novo*, and also include individual manufacturers of starting reagents, incubation times, concentrations, cell types, and assays for inhibitory capability. Baracchini clearly teaches one of ordinary skill how to screen for inhibitory compounds.

While Taylor indicates a high level of success may be expected by one of ordinary skill without providing voluminous detail, the teachings of Baracchini clearly combine with this to indicate that one of skill could reasonably expect success using published methodologies.

Finally applicants suggest that Baracchini et al. does provide a detailed blueprint for inhibiting MRP, but that no suggestion is contained therein that these methods may be applicable to other mRNA transcripts. First, Taylor indicates that methods of inhibition will work with any transcript--see introduction of Taylor. Second, Baracchini does provide indication that the teachings contained therein apply in a broader context:

> "Oligonucleotides have recently become accepted as drugs for the treatment of disease states in animals and man. For example, workers in the field have now identified antisense, triplex and other oligonucleotide therapeutic compositions which are capable of modulating expression of genes implicated in viral, fungal and metabolic diseases. Numerous antisense oligonucleotide drugs have been safely administered to humans and a number of clinical trials are presently underway. Efficacy has been demonstrated for several oligonucleotide drugs, directed to both viral and cellular gene targets. It is thus established that oligonucleotides can be useful therapeutics.
>
> "Targeting" an oligonucleotide to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins with the identification of a nucleic acid sequence whose function is to be modulated. This may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid from an infectious agent."

It is maintained that between Taylor et al., who indicates that any gene may be inhibited so long as the sequence is known, and Baracchini et al., who teasches how to design and screen molecules for specific levels of inhibitory activity, complete with precise protocols of how to make and use antisense oligos to inhibit a gene of known sequence, including materials related to synthesis of such oligos *de novo*, and also include individual manufacturers of starting reagents,

incubation times, concentrations, cell types, and assays for inhibitory capability, that one of skill could reasonable expect to have success in screening for molecules that inhibit Ship-1. Accordingly, the rejection is maintained.

No claims are allowed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 11, 12, and 14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hiatt et al. (U. S. Patent Number 6,136,568).

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridize with and inhibit the expression of Ship-1 of SEQ ID NO: 3, or compounds at least 8 nucleobases long that bind to an active site of said Ship-1, and to compositions comprising said compound and pharmaceutically acceptable carriers.

Nucleobases 1-9 from SEQ ID NO: 3 of Hiatt possesses 100% complementarity to the target region of applicants elected SEQ ID NO: 21 of the instant application, and would thus specifically hybridize with said target. Although this reference does not specifically teach the

function of inhibiting Ship-1 as claimed in the present application, the above-listed compound of the prior art meets all the structural limitations as set forth in the instant claims. Furthermore, this fragment was disclosed as useful in PCR that is carried out in suitable buffers, which are also considered to be pharmaceutically acceptable as diluents. Because the sequence and compounds meet all the structural limitations of the instant claims, they are considered to be substantially identical to applicant's claimed compounds, and in the absence of evidence to the contrary the sequence and compounds of the prior art are thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of Ship-1. Support for this conclusion is drawn from MPEP § 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of the above claims of the instant application are considered anticipated and/or obvious as outlined above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-24 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Rohrschneider *et al.*, in view of Ware *et al.,* Taylor et al., and Baracchini et al. (all of record).

The invention of the above claims is drawn to antisense compounds 20 to 50 nucleobases long that target Ship-1 of SEQ ID NO: 3, or said compounds comprising internucleoside, nucleobase, and 2' modifications, chimeras, or compositions comprising said compounds and pharmaceutically acceptable diluents thereof.

Rohrschneider et al. teach antisense compounds that target Ship-1. Furthermore, Rohrschneider et al. teach antisense compounds comprising phosphorothioate and other modifications or compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Rohrschneider *et al.* do not teach antisense sequences comprising specific nucleobase, and 2' modifications, chimeras.

Ware et al. teach the cDNA sequence encoding Ship-1 of applicants disclosed SEQ ID NO:3.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds 20 to 50 nucleotides long that comprise sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to screen for successful gene inhibition.

It would have been obvious to one of ordinary skill in the art to use the Ship-1 specific antisense sequences of Rohrschneider *et al.*, and modify them to be the specific length required in the instant claims, i.e. 20 to 50, and to make such compounds that inhibit to the 40% level as taught by Taylor *et al.* and Baracchini et al. for inhibition of Ship-1 expression. One would have been motivated to create such compounds because Rohrschneider et al. expressly teach

phosphorothioate-modified antisense compounds directed to the Ship-1 target, and because Baracchini *et al.* teach the same antisense oligo lengths as instantly claimed, and teach that such lengths are preferred. Baracchini also teaches inhibition of target of at least 40%. Finally, one would have a reasonable expectation of success given that Ware teaches the cDNA sequence of Ship-1 (applicants' SEQ ID NO:3) for designing antisense oligos against any portion of the gene, and further because Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and finally since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene and methods of screening for successful gene inhibition, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD